Haptoglobin and hemoglobin in subarachnoid hemorrhage: A tale of 2 globins

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EDITORIAL

Haptoglobin and hemoglobin in subarachnoid hemorrhage

A tale of 2 globins

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Although the incidence is declining, subarachnoid hemorrhage (SAH) continues to exact a substantial toll on society, with an estimated 20,000 aneurysmal SAHs (aSAHs) a year in the United States.[1] Outcomes have improved, but the mortality remains ≈35%, and half of the survivors cannot return to their previous level of functioning.[2] The most important prognostic factors for outcome are the neurologic condition of the patient on admission to hospital, the patient's age, and preexisting hypertension.[3] aSAH has a unique biphasic course, with initial or early brain injury (reflected in the neurologic condition) and a delayed phase of brain injury called delayed cerebral ischemia (DCI). Subarachnoid blood and specifically the erythrocytes and their main content, hemoglobin, appear to mediate DCI in humans. Extravascular free hemoglobin and iron released from it, whether into the CSF or the brain, are highly inflammatory and cytotoxic oxidants.[4] The body has developed ways to mitigate this, including synthesis of haptoglobin, which binds free hemoglobin, abrogating its toxicity. Therefore, clearing away the hemoglobin more quickly or preventing its deleterious effects by binding hemoglobin may decrease brain injury and improve patient outcomes from SAH.

Humans have 2 haptoglobin alleles, haptoglobin 1 and 2, that differ in their scavenging ability.[4] Of the 3 possible genotypes, the haptoglobin 2-2 genotype may have reduced scavenging and has associations with more severe phenotypes of diseases such as diabetes mellitus, cardiovascular disease, and renal failure.[4] Patients with haptoglobin 2-2 appear more likely to develop elevated transcranial Doppler intracranial arterial flow velocities, an indicator of vasospasm of the intracranial arteries after SAH,[5] although subsequently published data conflict on the role of haptoglobin genotype plays in SAH outcome.

In this issue of *Neurology*®, Gaastra et al.[6] performed an important study by collecting a large dataset that includes haptoglobin genotypes and outcome after aSAH. The fact that the authors collected 6 unpublished datasets along with 5 published ones demonstrates important collaborations with the authors.[6] The rigorously performed individual patient–level meta-analysis of these 939 patients, however, showed no evidence for any effect of haptoglobin genotype on the prespecified outcomes, including functional outcome, short-term complications of aSAH such as cerebral infarction, DCI, angiographic vasospasm, and transcranial Doppler flow velocities.

What reasons underlie this lack of association? Haptoglobin genotype may not influence the outcome. On the other hand, aSAH is a complex disease with many different patient-, disease-, and treatment-related factors contributing to patient outcome, again requiring large datasets to detect small prognostic effects. For example, treatment intensity may obviate the effects of haptoglobin genotype. Moreover, the modified Rankin Scale or Glasgow Outcome Scale scores dichotomized into favorable and unfavorable outcome—a rather blunt outcome assessment—may not have adequate sensitivity to detect small changes in patient outcome. In summary, this study demonstrates that if haptoglobin genotype does

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have an effect on outcome, the effect size would be small and most probably not clinically relevant.

Roughly 4.5×10^{19} molecules of hemoglobin are released from the typical aSAH volume of ≈35 mL into the ≈50-mL subarachnoid space, with each hemolyzing erythrocyte releasing 250 million molecules.[7,8] As an acute-phase reactant, the concentration of haptoglobin in the CSF, normally ≈0.06 mg/dL, would increase but would likely still be overwhelmed. Little is known about the concentrations of haptoglobin or of the different proteins resulting from the different genotypes in the CSF and brain after SAH; this remains an important area for additional work.

This study clearly demonstrates the large numbers of patients required to move the field along and highlights the need for national and international collaborations. Finally, as the authors mention, different studies collect different variables, use different definitions, and follow up patients for varying times. Common data elements are going to be key in the efforts to study large numbers of patients with aSAH.

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